Cardiovascular dysfunction in septic shock

RJ Snell and JE Parrillo

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Cardiovascular Dysfunction in Septic Shock*

R. Jeffrey Snell, M.D. and Joseph E. Parrillo, M.D.

(Chest 1991; 99:1000-09)

EDVI = end-diastolic volume index; LVEF = left ventricular ejection fraction; LVSWI = left ventricular stroke-work index; MDS = myocardial depressant substance; SVR = systemic vascular resistance; TNF = tumor necrosis factor

Septic shock has been increasing in incidence since the 1930s and is presently the most common cause of death in intensive care units (ICUs) in the United States. Reasonable current estimates of annual incidence are 400,000 cases of sepsis, 200,000 bouts of septic shock, and 100,000 deaths due to this syndrome. Reasons underlying this rising incidence and continued high mortality include increased use of cytotoxic and immunosuppressive drug therapies, increased patient age, increased presence of concomitant medical illnesses, increased use of invasive devices for diagnosis and therapy, and rising incidence of infections due to organisms other than Gram-negative bacteria (Gram-positive bacteria, fungi, and possibly viruses), and, perhaps, the emergence of antibiotic-resistant organisms. All estimates suggest that these numbers will continue to rise.

Septic shock is traditionally classified as the prototypic example of distributive shock (Table 1). A severe decrease in systemic vascular resistance (SVR) and generalized blood flow maldistribution develop in almost all affected patients. After aggressive volume loading to ensure adequate preload, the cardiac output is initially normal or elevated in more than 80 percent of patients with septic shock. This is in contrast to the cardiogenic, extracardiac obstructive, and oligemic (hypovolemic) forms of shock, which produce the acute phase of the shock syndrome via a decrease in cardiac output.

During the past several years, however, abnormalities of cardiac performance have also been clearly demonstrated during human septic shock. While cardiac output and stroke volume are usually well maintained during the initial stages of human septic shock, these parameters are very sensitive to small changes in ventricular preload and afterload. Better measures of intrinsic cardiac performance were needed to evaluate myocardial function in human sepsis. With the use of radionuclide-gated blood pool scanning and simultaneous catheter-derived thermodilution hemodynamics, highly accurate measurements of both ventricular performance and volumes could be obtained. The radionuclide-determined ejection fraction is relatively unchanged by acute changes in preload and afterload. Human studies utilizing these techniques demonstrated that the characteristic pattern of septic shock consists of an initial decrease in left ventricular ejection fraction (LVEF) occurring within 24 h of septic shock onset associated with an increase in both end-diastolic and end-systolic volume indices (Fig 1). This pattern of decreased LVEF and ventricular dilatation was found to be most characteristic of survivors during the initial few days of the disease.

*From the Department of Medicine, Section of Cardiology, Rush-Presbyterian-St. Luke's Medical Center and Rush Medical College, Chicago.

Reprint requests: Dr. Parrillo, Rush-Presbyterian St. Luke’s Medical Center, 1653 West Congress Parkway, Chicago 60612

<table>
<thead>
<tr>
<th>Classification of Shock</th>
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<tr>
<td>Cardiogenic</td>
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<tr>
<td>Myopathic (reduced systolic function)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Myocardial depression in septic shock</td>
</tr>
<tr>
<td>Mechanical</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
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<tr>
<td>Ventricular aneurysm</td>
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<tr>
<td>Severe left ventricular outflow obstruction (aortic stenosis, hypertrophic cardiomyopathy with obstruction)</td>
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<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Extracardiac obstructive</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
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<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Pulmonary calcification (massive)</td>
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<tr>
<td>Severe pulmonary hypertension (primary or Eisenmenger)</td>
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<tr>
<td>Coarctation of the aorta</td>
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<tr>
<td>Oligemic (hypovolemic)</td>
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<tr>
<td>Hemorrhage</td>
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<tr>
<td>Fluid depletion</td>
</tr>
<tr>
<td>Distributive</td>
</tr>
<tr>
<td>Septic shock</td>
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<tr>
<td>Response to toxic products (e.g. overdose)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Neurogenic</td>
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<tr>
<td>Endocrinologic</td>
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The pathogenetic mechanisms underlying this cardiovascular dysfunction are very complex (Fig 2). The sequence begins with a nidus of infection leading either to bloodstream invasion or release of large amounts of various mediators into the circulation. These mediators may consist of microorganism-elaborated exotoxins; microorganism-derived structural components, such as endotoxin and teichoic acid antigens; or host-manufactured products, such as...
cytokines (e.g., tumor necrosis factor [TNF], interleukins), complement components, and others. Although some of these mediators are more important than others, there are probably 20 or 30 molecular substances that can exert profound effects on the peripheral and pulmonary vasculature, and some substances (e.g., myocardial depressant substance) that appear to have direct myocardial effects. These vascular and myocardial abnormalities combine to produce generalized “cardiovascular insufficiency.” Aggressive therapy in patients with septic shock will reverse this process in approximately 50 percent, and these patients will survive.1-3 Unfortunately, the other 50 percent will not respond, but will die as a result of the mechanisms shown in Figure 2.

Unresponsive hypotension is usually due to a very low SVR, which cannot be corrected by any therapy; only a small proportion (approximately 10 to 20 percent) of cases of unresponsive hypotension are due to low cardiac output (decompensated myocardial depression). Multiple organ system dysfunction commonly affects the lungs, kidneys, liver, central nervous system, and heart. Ultimately this process leads to death due to failure of one or more organ systems.1,2,9

Investigations regarding cardiovascular dysfunction in septic shock have included laboratory work, experiments in animal models, and human studies. This article will review some of the recent data obtained from investigations designed to elucidate better the pathogenesis and therapy of this disease.

**CARDIAC DYSFUNCTION IN HUMAN SEPSIS: RECENT STUDIES**

The most common effect of sepsis on the cardiovascular system is to produce a hemodynamic profile characterized by an elevated cardiac index and decreased SVR. While some early studies in humans with septic shock reported a low cardiac index,10-12 it is likely that many of the patients had an inadequate ventricular preload, since the central venous pressure was used at that time to evaluate volume status. With use of the pulmonary capillary wedge pressure as a measure to ensure an adequate left ventricular preload, a low cardiac index has been found to be quite uncommon, even in the very late stages of septic shock.3

In addition to this hyperdynamic hemodynamic profile, reversible depression of LVEF and dilation of the left ventricle usually occur in human sepsis (Fig 1). This pattern of cardiovascular performance was recently extended to the right ventricle.13 Table 2 shows the initial and final left and right ventricular ejection fractions and end-diastolic volume index (EDVI) in 22 survivors and 17 nonsurvivors of septic shock. Both LVEF and right ventricular ejection fraction are initially low, and both ventricles are dilated. These values return toward normal in survivors. Thus, the myocardial depression of septic shock is a biventricular phenomenon.

The response to volume infusion is also abnormal in patients with septic shock, providing further evidence of depressed ventricular performance. A recent study14 examined the response to fluid administration in three groups of patients: critically ill nonseptic

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**Table 2—Hemodynamic Variables in Survivors and Nonsurvivors of Septic Shock**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 22)</th>
<th>Nonsurvivors (n = 17)</th>
</tr>
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<tbody>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.31</td>
<td>0.47</td>
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<tr>
<td>Left ventricular end-diastolic volume index, ml/m²</td>
<td>145</td>
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<tr>
<td>Right ventricular ejection fraction</td>
<td>0.35</td>
<td>0.51</td>
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<tr>
<td>Right ventricular end-diastolic volume index, ml/m²</td>
<td>124</td>
<td>88</td>
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</table>

†Paired-sample t test.

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**Figure 3. Frank-Starling relationships for each of the three patient groups. Data points represent mean prevolume and postvolume infusion values of end-diastolic volume index (EDVI) and left ventricular stroke work index (LVSWI) for each patient group. (From Ognibene et al. Chest 1988; 93:903-100. Reproduced by permission.)**
control patients, patients with sepsis without hypoten-
sion, and patients in septic shock (Fig 3). All groups
received similar amounts of fluid and had similar
increments in pulmonary capillary wedge pressure.
In control patients, volume infusion led to substantial
increases in both EDVI and left ventricular stroke-
work index (LVSWI), changes representing a normal
response. Patients with septic shock had a dilated
ventricle prior to volume challenge, and they had a
markedly diminished cardiac response to volume
administration with only minor increments in both
EDVI and LVSWI. The septic patients without hy-
potension demonstrated an intermediate response.
These Frank-Starling relationships further confirm
altered ventricular performance, as measured here by
changes in LVSWI in response to volume loading, in
patients with septic shock.

Serial measurements of some of the cardiovascular
variables mentioned have been studied in an attempt
to identify factors of prognostic value during the early
stages of septic shock. In a study of traditional hemo-
dynamic parameters,3 the statistically significant pre-
dictors of survival included an initial heart rate of
<106 beats per minute, a 24-h heart rate of <95
beats per minute, or systemic vascular resistance of
>1,529 dynes·s·cm·⁻⁵·m², and a change over the initial
24 h manifested by a decrease in heart rate by >18
beats per minute or a decrease in cardiac index by
>0.5 L/min·m². These findings suggest that nonsur-
ivors have a persistence of the hyperdynamic hemo-
dynamic profile, while the survivors’ hemodynamic
values begin to return toward normal by 24 h.

Serial changes in LVEF and EDVI have also been
shown to distinguish survivors of septic shock from
nonsurvivors.4 In that study, a control group of critically
ill nonseptic patients was used. The survivors initially
had a depressed mean LVEF of 0.40 compared with
the control patients’ ejection fraction of 0.53. This was
associated with a dilated left ventricle (EDVI = 122
ml/m² compared with a control value of 90 ml/m²).
These abnormalities persisted for the first two to five
days and then returned toward normal by one to two
weeks after the onset of septic shock. Nonsurvivors,
on the other hand, had an LVEF and an EDVI that
were not significantly different from those of the
control patients and that did not change significantly
over the course of their septic shock. In addition, in
survivors there was a strong negative correlation
between LVEF and EDVI (r = -0.62, p < 0.001),
whereas no such statistically significant correlation
occurred in nonsurvivors. In other words, in the
nonsurvivors, a decrease in LVEF was not consistently
associated with left ventricular dilatation. Thus, ven-
tricular dilatation may in part be a normal compensa-
tory mechanism, and a ventricle that is unable to
dilate may predispose to a higher mortality in human
septic shock.

Two different hypotheses have been offered to
account for the myocardial depression in sepsis. The
first postulated mechanism is that coronary hyperper-
fusion leads to ischemic myocardial dysfunction. Ar-
guments for this mechanism have been based on
animal models that were hemodynamically very dif-
ferent from human sepsis.15,16 A recent study investig-
gated the coronary circulation during human septic
shock using coronary sinus thermodilution catheters
to measure coronary sinus blood flow and myocardial
lactate extraction.17 The patients with septic shock had
coronary blood flows equal to or greater than those of
controls. In addition, there was no difference in
myocardial lactate extraction between patients with
septic shock and myocardial depression and those with
sepsis but no myocardial depression. Taken together,
these findings exclude global ischemia as the cause of
myocardial depression in septic shock. These findings
were corroborated in a subsequent study.18

A second postulated mechanism is the presence in
the bloodstream of one or more active circulating
myocardial depressant substances (MDSs). As with
earlier studies of coronary perfusion, most early
investigations of circulating MDS activity employed
sera from animal models of questionable human rele-
ance.19,20 Furthermore, these studies utilized isolated
papillary muscle preparations to assay MDS activity,
assays that were difficult to establish and reproduce.
Clearly, evaluation of the role of MDSs in human
sepsis would benefit from a less cumbersome in vitro
myocardial contractility assay that could be correlated
with in vivo measurements of cardiac performance.

In Vitro Studies of Myocardial Depression

In 1985 a biologic system for assaying MDS activity
in human serum with use of newborn rat myocytes in
primary tissue culture was reported.41 These myocytes
adhere to the bottom of a petri dish and after several
days of growth they exhibit spontaneous contractions
at rates of 30 to 100 beats per minute. Videodensi-
tometry was used to evaluate the movement of the
cell, permitting quantitative recording of the extent
and velocity of shortening during a single myocyte
contraction. This system allowed serum to be assayed
for effects on myocardial cell contractility. When
newborn rat myocytes were exposed in vitro to sera
from patients in the acute phase of septic shock, the
extent and velocity of myocyte shortening were de-
pressed significantly (Fig 4).41 The degree of depres-
sion in vitro correlated with the amount of decrease
in LVEF in vivo. Furthermore, this in vitro depression
did not occur with sera from normal volunteers, crit-
ically ill nonseptic patients, or patients with reduced
ejection fractions due to structural heart disease; nor
was depression seen with sera taken from the patients

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during the recovery phase of septic shock. These findings provided the first strong evidence that circulating MDSs play a pathophysiologic role in the myocardial dysfunction of human septic shock.

The assay system has since been revised by placing latex beads onto the cultured myocytes, allowing the use of a video closed-loop-tracking system to quantify myocyte shortening with greater ease than videodensitometry. Instantaneous movement of the latex bead is tracked electronically and converted to an analog signal. Experiments utilizing this modified assay system have confirmed the initial results and provided further clinical correlations.

In one study, sera from 34 consecutive patients with septic shock were assayed for MDS activity. A patient was considered positive for MDS if his serum consistently depressed myocyte contractility by 20 percent or more; almost half (43 percent) of the patients with septic shock in this series were positive for MDS. As in the 1985 study by Parrillo et al., in vitro depression of myocardial cell contractility correlated with in vivo depression of ejection fraction. Further, MDS-positive patients had higher pulmonary artery wedge pressures and larger EDVI values than MDS-negative patients (Table 3). In addition, MDS-positive patients had higher mean peak lactic acid levels, suggesting greater inadequacy of tissue blood flow or perhaps a direct mediator-induced peripheral vascular effect. High levels of MDS activity were found in sera from a high percentage of patients with septic shock, particularly those with the most severe cardiovascular insufficiency. The presence of MDS activity is also associated with a trend toward increased mortality (36 percent mortality in MDS-positive vs 10 percent in MDS-negative patients) in this study.

Recent attention has focused on the nature and identity of this MDS. Previous experiments have shown a number of specific characteristics. As the concentration of depressant serum placed onto

### Table 3—Characteristics of 14 Patients with MDS and 20 Patients without MDS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MDS-positive (n = 14)</th>
<th>MDS-negative (n = 20)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Plasma lactate, mmol/L</td>
<td>6.9 ± 1.7</td>
<td>2.7 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonary artery wedge pressure, mm/Hg</td>
<td>17 ± 2</td>
<td>12 ± 1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DVI, ml/m²</td>
<td>162 ± 16</td>
<td>118 ± 10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>28 ± 3</td>
<td>39 ± 3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*All values are expressed as mean ± SE. (Adapted from Reilly et al. Chest 1989; 95:1072-80. Reproduced with permission.)
+Determined two to four days after the onset of septic shock.
myocytes is increased in a stepwise manner, there is a concentration-dependent decrease in both the extent and velocity of myocardial cell contraction. Depressant activity is water soluble and will not diffuse through a dialysis membrane. Recent molecular filtration experiments with Amicon filters suggest that MDS is a moderate-size molecule weighing at least 10,000 d.23

Most recently, the myocyte assay has been used to study the activity of several possible mediators of septic shock.24 Purified preparations of interleukin-1, interleukin-2, and endotoxin produced no depression of myocyte contraction even in concentrations substantially higher than those measured during human septic shock. However, TNF at a dose of 250 units/ml did produce significant depression of myocyte shortening, with a mean decrease of 24 percent. Thus, TNF may be one of several molecules that directly produce the myocardial depression of human septic shock. Experiments attempting to further identify such molecules utilizing this in vitro assay are ongoing.

A Canine Model of Septic Shock

Further investigation into the nature of myocardial depression in sepsis required the development of an appropriate animal model. Previous animal models were modified to produce one that more closely simulates the cardiovascular pattern of human septic shock.25 In this model, live bacteria contained in a fibrin clot are implanted surgically into the peritoneum as a nidus of infection, leading to sustained bacteremia in all animals. Serial hemodynamic assessments were performed in conscious, unsedated animals both before and after volume loading, using arterial and pulmonary artery catheters and simultaneous radionuclide ventriculography. With this model, hypotension occurred at 12 to 24 h. Two to four days after sepsis onset, a substantial decrease in LVEF developed. With adequate volume loading, animals manifested left ventricular dilatation, high cardiac output, and low SVR. In surviving animals, these hemodynamic changes returned toward normal in seven to ten days. This time course and cardiovascular pattern are remarkably similar to those of human septic shock.5

In further studies, the canine model demonstrated a relationship between the number of organisms placed into the nidus and the amount of myocardial depression. Increasing doses of bacteria corresponded to progressive decreases in LVEF and progressive downward shifts on both Frank-Starling and end-systolic volume/pressure left ventricular function plots.26 Some types of bacteria (despite equivalent doses) were more potent inducers of cardiovascular changes and lethality. However, all bacteria (whether Gram-positive or Gram-negative, viable or nonviable) produced the same general pattern of cardiovascular insufficiency.27 The fact that structurally and functionally distinct bacteria and bacterial products induce the same pattern of cardiovascular injury strongly supports the presence of a final common pathway of cardiovascular insufficiency in septic shock. Recent investigations have utilized the canine model to study potential mediators of this common pathway. Endotoxin, a mediator known to trigger the release of a large number of other mediators, was placed into a fibrin clot and implanted into the peritoneum.28 The subsequent pattern of cardiovascular changes was identical to that previously described for septic shock induced by live organisms in the canine model.26 However, as was previously mentioned, experiments with Gram-positive organisms (with absent measured blood endotoxin levels) showed this same cardiovascular pattern.27 Thus, endotoxin is sufficient but not necessary to produce septic shock.

In other experiments testing possible mediators, TNF was infused intravenously into dogs and found to induce all of the progressive changes in cardiovascular function seen with viable bacteria (Fig 5).28 In a similar canine study, interleukin-1 was infused; however, in contrast to the TNF findings, high doses of interleukin-1 produced brief hypotension and none of the other sepsis-associated cardiovascular changes.29 Thus, as with the in vivo experiments, canine studies support the importance of TNF as one of the major mediators of the final common pathway of cardiovascular insufficiency in septic shock.

Human Responses to Possible Mediators

With the establishments of a clear pattern of cardiovascular dysfunction in septic shock and preliminary data on probable mediators from in vitro and canine work as background, recent investigation has focused on mediator effects in humans.

While endotoxin has been administered to humans in clinical or research settings for years to evaluate a variety of clinical responses, limited information is available defining its effects on the human cardiovascular system. Hence, a recent study was performed during which the cardiovascular response to endotoxin administration was evaluated in normal humans by monitoring with radial and pulmonary artery catheters and nuclear heart scans.30 After evaluating the initial effects of endotoxin for 3 h, each volunteer received a volume infusion to simulate the clinical management of sepsis and to evaluate ventricular performance in response to increased preload.

The core temperature rose and peaked by 3 to 4 h following endotoxin administration. At 3 h, the cardiac index and heart rate rose and the SVR fell compared with control values.30 The LVEF fell below baseline and below that of the similarly treated control patients.
Figure 5. Serial mean changes (±SE) in ejection fraction, EDVI, and end-systolic volume index in dogs challenged intravenously with TNF. Solid lines connect mean hemodynamic values in serial dogs. Dashed arrow indicates response to volume for each group of dogs. (From Natanson et al. J Exp Med 1989; 169:823-32. Reproduced with permission.)

At 5 and 6 h following endotoxin administration. The left ventricular EDVI and end-systolic volume index increased. Ventricular performance was also described with use of the load-independent relationship of peak systolic pressure to end-systolic volume index, comparing changes from baseline to maximum fluid loading in endotoxin and control groups. The change in this ratio was abnormal in the subjects who received endotoxin (Fig 6, panel D). Left ventricular function was further evaluated by measuring the stroke volume index and LVSWI normalized to the end-diastolic volume (Fig 6, panels B and C). These data demonstrate reduced systolic performance during endotoxemia independent of preload and afterload. Furthermore, the left ventricular pressure to volume ratio was reduced, suggesting that ventricular compliance may have increased after endotoxin administration (Fig 6, panel A). Follow-up echocardiograms at 24 and 48 h after endotoxin administration revealed no persistent abnormalities.

Thus, the cardiovascular changes following endotoxin administration to normal humans were qualitatively similar to those seen in clinical septic shock: a hyperdynamic cardiovascular state with a depressed and dilated left ventricle and abnormalities of ventricular performance and volume that were reversible.

Other evidence has implicated endotoxin as a major mediator of human septic shock as well. Endotoxin has biologic effects analogous to those observed during septic shock: it has been shown to cause fever,
interleukin-1 and TNF release, complement activation, disseminated intravascular coagulation, and shock in animals.\textsuperscript{31} Further, naturally occurring antibodies to endotoxin are associated with increased survival in Gram-negative septic shock in humans.\textsuperscript{32} In addition, it has been demonstrated that immune plasma from volunteers vaccinated with the \textit{Escherichia coli} J5 mutant prevented death in patients with Gram-negative septicemia.\textsuperscript{33} Recent human trials employing monoclonal antibodies to lipid A, the toxic component of endotoxin, have shown efficacy in reducing the mortality of Gram-negative bacteremia.\textsuperscript{34} However, several areas of investigation speak against endotoxin as the exclusive or dominant mediator of human septic shock. Endotoxin alone did not produce consistent myocardial depression in the in vitro assay discussed previously.\textsuperscript{35} In the canine model, other mediators (eg, TNF) were found to produce changes in cardiovascular function similar to those seen with endotoxin.\textsuperscript{36} Of note, in the human study, TNF functional activity rose and fell following endotoxin administration.\textsuperscript{37} However, these changes temporally preceded the alterations in cardiac systolic and diastolic function that occurred at 5 to 6 h following endotoxin administration, suggesting either a delayed effect of TNF activity on cardiac function or the generation of other cardiodepressant mediators during endotoxemia.\textsuperscript{38} In another human study, interleukin-2 (a cytokine being used in antitumor immunotherapy) was found to induce multiple reversible cardiovascular abnormalities that are similar to the hemodynamic manifestations of human septic shock,\textsuperscript{39} suggesting a possible role for this mediator as well. Finally, direct measurement of circulating endotoxin has not consistently correlated with the clinical manifestations and outcome of Gram-negative septicemia.\textsuperscript{40}

In an effort to clarify the incidence and significance of endotoxemia in humans, a recent study determined serial endotoxin levels every 4 h for 24 h in 100 consecutive patients admitted to an ICU with septic shock.\textsuperscript{41} Blood endotoxin was measured with a sensitive chromogenic limulus amebocyte lysate assay. Detectable endotoxemia was found in 43 patients; however, only 20 of the 43 patients with endotoxemia had a positive limulus assay on initial determination. The level of endotoxin in many of these patients would not have been detectable with the older limulus gelation assay. In addition, endotoxemia often occurred intermittently, underscoring the need for frequent serial sample collection. The presence of endotoxemia was correlated with blood culture positivity (54 percent vs 25 percent, \textit{p}<0.01), lactic acid level (5.5±0.8 vs 3.0±0.3 mmol/L, \textit{p}<0.005), low SVR (456±30 vs 582±33 dyne·s·cm\textsuperscript{-5}, \textit{p}<0.05), and a depressed radionuclide determined LVEF (34±2 percent vs 45±2 percent, \textit{p}<0.001). In the subgroup of patients with septic shock and positive blood cultures (\textit{n}=37), endotoxemia was associated with a higher mortality (39 percent vs 7 percent, \textit{p}<0.05). Of note, only 26 percent of the endotoxin-positive patients had Gram-negative bacteremia, suggesting that endotoxemia may play a pathogenetic role in many cases of clinical septic shock even when Gram-negative organisms are not isolated from the blood.

When all these data are analyzed, as was true with canine data, it appears that endotoxin is probably sufficient but not necessary to produce septic shock in humans. Most likely it is one of several important mediators of this process (Fig 2).

**Therapeutic Implications**

Much of this research into the patterns and mechanisms of myocardial dysfunction in septic shock has implications for therapy of this complicated disease.

Optimal treatment for patients with septic shock involves prompt diagnosis and initiation of therapy, aggressive hemodynamic monitoring, and management in an ICU. Several retrospective studies have demonstrated a decreased mortality for septic shock patients who are cared for in a modern ICU setting.\textsuperscript{42} This environment permits physicians to use invasive techniques, including indwelling peripheral and pulmonary artery catheters to rapidly detect hemodynamic, respiratory, and acid-base changes and to initiate appropriate therapy.

Volume resuscitation with hemodynamic monitoring should be one of the first therapeutic steps in the management of patients with septic shock. However, as was discussed previously, patients with septic shock have a markedly diminished myocardial response to volume infusion.\textsuperscript{14} Hence, hypotension frequently persists, necessitating the addition of vasopressor agents.

If a patient in septic shock remains hypotensive after volume has raised the pulmonary artery wedge pressure to 15 to 18 mm Hg, then dopamine should be added for its inotropic and vasopressor capability to raise the mean blood pressure to at least 60 mm Hg. If the dopamine dose required to achieve this goal exceeds 20 \textmu g/kg/min, another vasopressor, typically norepinephrine, is begun. Dobutamine may be added to enhance cardiac inotropy in patients with evidence of profound myocardial depression.

The use of norepinephrine in patients in septic shock who fail to respond to dopamine has been a controversial topic. Some investigators have voiced concern that this potent vasoconstrictor might worsen the shock syndrome in certain patients. However, recent data demonstrate that norepinephrine can reverse septic shock in patients unresponsive to both volume and dopamine.\textsuperscript{43,44}

Of note, the effects of norepinephrine with and
without dopamine on renal blood flow were assessed in a canine model.\textsuperscript{43} The addition of dopamine to pressor doses of norepinephrine resulted in significantly higher renal blood flow and lower renal vascular resistance than norepinephrine infusions alone. In the clinical setting, patients requiring therapy with norepinephrine to support blood pressure may benefit from the simultaneous administration of low-dose dopamine (approximately 1 to 4 µg/kg/min) to increase renal blood flow. Once blood pressure is normalized with norepinephrine, the lowest dosage that maintains blood pressure should be utilized to minimize any potential vasoconstrictor effects on organ blood flow. Overall survival in norepinephrine-treated patients is approximately 40 percent, a substantial survival rate for such a critically ill patient group.

In addition to hemodynamic support, other therapy for septic shock is critical. Prompt initiation of an empiric antibiotic regimen that includes an agent effective against the subsequently identified microorganisms has been associated with improved survival and decreased frequency of shock.\textsuperscript{44,45} Clearly, it is essential that broad-spectrum antibiotic coverage be started immediately pending culture results.

High-dose corticosteroid therapy has also frequently been advocated for treatment of septic shock based on efficacy in some animal models. Recently, however, three large clinical trials have revealed no difference in mortality in corticosteroid-treated patients compared with control patients.\textsuperscript{46-48} In addition, these data demonstrate an inability of corticosteroids to prevent or reverse shock, as well as the occurrence of superinfections in corticosteroid-treated patients. Based on these studies, corticosteroid therapy in patients in septic shock should be reserved only for suspected or documented adrenal insufficiency.

Many of the recent clinical investigations into therapy have focused on the inhibition of the mediators of the toxic process involved in the septic shock cascade (Fig 2). Antihistamines have not proved effective, and recent studies have failed to document elevated histamine levels during human septic shock.\textsuperscript{49,50} Although arachidonic acid metabolites may account for some of the vascular effects of sepsis, inhibition of eicosanoids has not been shown to be therapeutically useful to date. Some animal models of shock are very dependent on endorphins; however, clinical trials using naloxone to inhibit endorphin receptors have not convincingly shown efficacy. On the other hand, inhibition of endotoxin by use of antisera has been associated with improved survival from Gram-negative bacteremia.\textsuperscript{51} This remains an area of active investigation. Several very recent trials employing monoclonal antibodies against endotoxin have shown promise of efficacy in patients with Gram-negative sepsis.\textsuperscript{52}

Continued research into the pathogenesis of septic shock should allow the continued development of the best supportive strategies, as well as specific measures directed against key steps in the process, which should in turn lead to further reductions in the high mortality from this disease.

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